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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,199	09/10/2003	Stephen M. Allen	BB1157USCNT	5569

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,199	ALLEN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2006 and 30 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 August 2006 has been entered.

2. Claims 26-29 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The objection to claim 26 is withdrawn in light of Applicant's amendment of the claim.

Claim Rejections - 35 USC § 112

5. Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding a SEQ ID NO:18 and constructs and vectors comprising them, does not reasonably provide enablement for nucleic acids encoding a protein with 90% identity to SEQ ID NO:18 and constructs and vectors comprising them. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 8 March 2006. Applicant's arguments filed 31 August 2006 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding a protein with 90% identity to SEQ ID NO:18 and constructs and vectors comprising them.

The instant specification, however, only provides guidance for cDNA libraries from a number of plants and plant tissues, including wheat developing kernel, and sequencing the inserts from an unknown number of the clones in these libraries (example 1), BLAST analysis of the cDNA sequences (example 2), identification of clones that have homology to the *Arabidopsis*, potato and corn brittle-1 homologs; the clones include SEQ ID NO:17, which encodes SEQ ID NO:18 (example 3). The specification also provides general guidance for the expression of chimeric genes in monocots (example 4), dicots (example 5), and microbes (example 6).

The instant specification fails to provide guidance for how to make or isolate nucleic acids encoding proteins with 90% identity to SEQ ID NO:18 - specific hybridization or PCR conditions, probes or primers are not recited. The instant specification fails to teach essential regions of the encoded protein. The instant specification also fails to provide guidance for how to use nucleic acids that encode proteins that have 90% identity to SEQ ID NO:18 but where the protein does not have adenylate translocator activity.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:18 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain adenylate translocator activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of

aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein.

Given the unpredictability and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate Brittle-1-encoding nucleic acids encoding proteins with 90% identity to SEQ ID NO:18. Making all possible single amino acid substitutions in an 432 amino acid long protein like that encoded by SEQ ID NO:17 would require making and analyzing 19^{432} (2.6×10^{552}) nucleic acids; these proteins would have 99.8% identity to SEQ ID NO:18. Because nucleic acids encoding proteins with 90% identity to SEQ ID NO:18 would encode proteins with 43 amino acid substitutions, many more than 2.6×10^{552} nucleic acids would need to be made and analyzed.

Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins with 43 amino acid substitutions that also have adenylate translocator activity would require undue experimentation.

Assaying this nucleic acid requires plant transformation. Sullivan et al (1995, Planta 196:477-484) teach that the full-length maize Brittle-1 coding region could not be expressed in *E. coli* (pg 478, left column, paragraph 3), and an adenylate translocator requires an intact membrane for assaying. As the specification does not describe the transformation of any plant with a nucleic acid encoding a protein with 90% identity to SEQ ID NO:18, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with altered starch, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant believes this is a rejection for the full scope of enablement (response pg 3).

This is not the case; this is a scope of enablement rejection. Nucleic acids encoding a SEQ ID NO:18 and constructs and vectors comprising them are enabled.

Applicant urges that a Clustal alignment of SEQ ID NO:18 with the maize brittle-1 protein of Sullivan and a potato protein identified in the specification as a brittle-1 protein shows homology and highly conserved motifs (response pg 3).

This is not found persuasive because the specification does not teach how to make nucleic acid encoding brittle-1 proteins with 90% identity to SEQ ID NO:18. The identity of SEQ ID NO:18 as a brittle-1 protein is not in question.

Applicant urges that the alignment shows close homology among the sequences and Appendix B shows percent identity; the alignment shows conservation of motifs and that SEQ ID NO:18 is a brittle-1 protein and is a mitochondrial carrier, citing Palmieri (response pg 4).

This is not found persuasive. The specification does not teach how to make nucleic acid encoding brittle-1 proteins with 43 amino acid substitutions relative to SEQ ID NO:18. The Palmeiri motif only provides a teaching for a small portion (27 amino acids) of the 433 amino acid long overall sequence. The structural elements required for *brittle-1* function are not taught.

Applicant urges that Appendix C shows the alignments of the three 100aa repeats based on a motif taught by Saraste, and Appendix D shows percent identity among these motifs, showing they are adenylate transporters, and there is a conserved secondary structure (response pg 4-5).

This is not found persuasive. No details can be made out in Table 1 of Saraste. It is not clear how the SEQ ID NO:18 motifs line up with those of Saraste. It is not clear how these motifs teaching how to make nucleic acid encoding brittle-1 proteins with 90% identity to SEQ ID NO:18, given they appears to a few amino acids in common.

Applicant urges that adenylate transclocator activity can be assayed in vitro by the method of Shannon using intact amyloplasts; thus, no plant transformation is required (response pg 5-6).

This is not found persuasive because making the intact amyloplasts comprising a proteins with 90% identity to SEQ ID NO:18 would require transforming a plants with the nucleic acid. Thus, screening of transformed plant is required. Such screening requires undue experimentation

in light of the lack of guidance in the specification as to which amino acid substitutions should be made.

6. Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 8 March 2006. Applicant's arguments filed 30 November 2006 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that encoding brittle-1 proteins with 90% identity to SEQ ID NO:18. In contrast, the specification only describes a coding sequence from wheat that comprises SEQ ID NO:17. Applicant does not describe other nucleic acids encompassed by the claims, and the structural and functional features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described nucleic acids that encode a protein with 90% identity to SEQ ID NO:18 within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that structural information consistent for brittle-1 proteins, including homology and conserved motifs, and activity assays were provided at the time of filing (response pg 3).

This is not found persuasive because neither the specification nor the prior art describe structures required for the *brittle-1* function, and the specification does not describe the structure of a brittle-1 protein with 43 amino acid substitutions relative to SEQ ID NO:18. The necessary and sufficient structural elements of a protein with *brittle-1* function are not described.

Conclusion

7. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Anne Kubelik, Ph.D.
February 15, 2007